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NIXON & VANDERHYE, PC			AUDET, MAURY A	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/553,324	<b>Applicant(s)</b> NEW, ROGER R. C.
	<b>Examiner</b> MAURY AUDET	<b>Art Unit</b> 1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 11/6/08.

2a) This action is FINAL.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 59-93 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) 73-82,92 and 93 is/are allowed.

6) Claim(s) 59-72 and 83-89 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All    b) Some \* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-156/08)  
Paper No(s)/Mail Date 11/08,9/08,7/08,6/08.

4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.

5) Notice of Informal Patent Application

6) Other: \_\_\_\_\_.

**DETAILED ACTION**

Applicant's response following the **Interview of 4/18/08** is acknowledged. The substance of the interview was as follows:

An interview was scheduled to go over the amended claims following the filing of the RCE. The Examiner indicated the case was formerly with Examiner Khanna, to which this Examiner maintained as Final his original action. The amended claims are drawn to both products and methods, both examined on the merits. The 112 1<sup>st</sup> written description issue appears to be obviated based on amendment, as the macromolecule in question is not the point of novelty, rather virtually any macromolecular active agent that passes the enteric cellular barrier is deemed contemplated for use in the aromatic alcohol (propyl gallate, BHA, BHT) oral composition.

The issue turned and focused on the obviousness issues surrounding the art of record and limitations claimed, including the open ended language thereto (particularly as concerns the product, oral composition comprising e.g. X and Y and anything else).

Regarding the products, the Examiner indicated that the intended use or effect of the compounds therein are not given patentable weight per se, but rather the limitations objectively analyzed v. that of the art. As to the use/effect, such arguments are more appropriately reserved for the method of use thereof.

As to the products, should art be maintained on the amended claims, claims 63 and 69 were reviewed as to possible claims for consideration that could be amended into the base claim (if found free of the art), should arguments of record not be found persuasive. Addressing the above will be carried out in the written record.

There is no need for Applicant to file an interview summary.

As previously noted, Applicant's amendment and filing of an RCE are noted, along with the response to the outstanding 112 1<sup>st</sup>/103 rejection are acknowledged.

The Written Description rejection has been reconsidered and is now withdrawn. However, the 35 USC 103 rejection has been maintained, though a new reference cited to further address the claims as amended, and the claims are still deemed obvious over the combination of references and teachings applied therein.

The present application has been transferred from former Examiner Khana to the present Examiner.

It was previously noted that applicant's arguments pertaining to the rebuttal of the general lack of unity inventive finding made by the Examiner is found persuasive. Based on the Applicant's arguments the Examiner has rejoined the method claims.

As noted previously, the filing of a Terminal Disclaimer over copending 10/553,169 is acknowledged.

Interview Summary of May 17, 2007

The Examiner acknowledges Applicant indicated that the interview summary with the former Examiner mistakenly did not incorporated in the record. The Examiner apologizes for this and thanks Applicant for providing a copy of that received to the Office. However, this Examiner does not yet feel the interview summary or amended claims have persuasively shown allowable subject matter. An overview and analysis of the interview summary is provided below:

1. "Amending the active macromolecular principle to read on polypeptides and protein. Only to overcome written description rejection."

This has not been done, the claims remains drawn to the polynucleotides/ nucleic acids and polysaccharides/carbohydrates. However, this Examiner is ok with this, noting that the macromolecule in question is not at issue, but rather the aromatic alcohol.

2. "Amending claims to read on an oral pharmaceutical composition and methods of using the pharmaceutical composition."

This has been done. However, new art of record, combined with the former art, is still deemed to render the amended claims obvious.

3. "Amending claims to define novelty of the composition to be permeable at low pH's."

This has not been. The claims are drawn to a range up to pH 7. This is neutral pH/homeostatic pH, naturally occurring within the body. Not "low pH".

4. "Deleting claims 45 and 56."

This has been done. However, new art of record, combined with the former art, is still deemed to render the amended claims obvious.

35 USC 103:

The following was noted in the previous action:

Regarding the issue of whether the present invention remains an unobvious contribution over the art, this Examiner is not yet convinced by the present amendments/arguments. Namely, that the prior art of record, combined with the ordinary skill of one in the art (a PhD chemist working in the field of oral peptide pharmaceuticals preparations), would not have motivated the skilled artisan to arrive at an enteric coated composition comprising ANY peptide or ANY derivative/analogue of certain known peptide genuses (inherently permeable at neutral pH of 7) AND a known aromatic alcohol (which inherently works as an absorption enhancer in the product). The functional effect of the alcohol in the product bears no patentable weight in regards to the mixing of peptides and alcohols in products. As to the method of enhancing absorption of such a product, aromatic alcohols are [not] known absorption enhancers, and the selection of known aromatic alcohols to carry out the same would have been merely a matter of routine optimization by the skilled artisan, if not taught/suggested by the prior art of record. Applicant has provided no substantive data or otherwise on the record to substantiate that the claimed alcohol has provided a clearly unexpected result over any other known alcohol as an absorption enhancer or over the teachings/suggestions within the prior art of record.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The rejection of claims 59-72 and 83-89 (THE PRODUCTS) under 35 U.S.C. 103(a) as being unpatentable over New (WO 02/28436) in view of New (USPN 5,853,748), either Wacher et al. I or II (US 6,180,666 or 5,962,522; also cited in the specification at p. 2), Chakravorty (WO 02/022158) and Ivanovic (Chromatographia (1995) 40:652-656) is maintained for the reasons of record.

Again, the instant claims are drawn to pharmaceutical compositions comprising an active molecular principle, an aromatic alcohol, a solubilization aid, and methods of enhancing the absorption of an active macromolecular principle comprising administering to a patient the above-mentioned pharmaceutical composition.

Applicant's arguments as to the products are not found persuasive based on the open-ended language ("COMPRISING"), in view of the art of record, and that the intended use or functionality of said PRODUCT, does not carry patentable weight by argument, here.

The rejection is repeated below for continuity of record, as applied to the PRODUCT

CLAIMS:

Applicant notes at the outset on p. 8 of the response that the amended claims are drawn to 1) an 'oral' composition; and 2) that includes a 'solubilization' aid. The Examiners acknowledges Applicant's arguments, filed as part of the RCE, along with the amended claims, have been fully considered but are not yet found persuasive. Although deemed moot, in light of the addition of a new reference over the amended claims, the Examiner does note that Applicant states on page 19 of the response that:

Nonetheless, *considering the Examiner's objection as a whole*, he seems to suggest the following chain of reasoning. BHT is known as an antioxidant (Chakravorty and Ivanovic). It is known that the amount of ionized vs unionized antioxidant determines pH (Ivanovic). It is known to use a pH buffer to enhance absorption in the digestive tract (New '748). Therefore it is obvious to use the antioxidant BHT to determine the pH and thereby enhance absorption. With respect, the applicant cannot accept this chain of reasoning.

As to the above, it is this rationale, under 103, that the combination 'as a whole' applies to the claimed subject matter, which the Examiner maintains substantially on the original grounds. Namely, the Examiner accepts that the references, alone (without each other), do not teach each and every limitation, hence the applied combination to provide the teachings/suggestions within the pharmaceutical preparation art, that the skilled artisans therein were aware of the various options available to make an aromatic alcohol oral composition (capable of delivering virtually any compound). Thus, as to the combination as a whole, the invention as claimed is still presently deemed *prima facie* obvious.

With respect to the composition claims 59-72 and 83-87, New ('28436) disclose compositions for oral administration comprising a macromolecule, such as insulin (Example 1) or heparin, further comprising an *aromatic alcohol, such as benzyl alcohol* (Example 1), wherein the comprises *comprises up to 75% by weight of the aromatic alcohol* (page 7, lines 25-30). New ('28436) also discloses *solubilization aids* such as amphiphiles (page 8, lines 15-20) to improve the solubility of the macromolecule in the aromatic alcohol. Further New ('28436) disclose that the compositions of active principal, alcohol and amphiphile can be co-dissolved in the aqueous phase or the water removed by lyophilization (page 10, lines 1-5). In addition New ('28436) disclose enteric capsule of the composition of the invention to withstand the conditions of the stomach, wherein the *enteric coating* becomes permeable at a pH from 5.5 to 7 (page 7, lines 10-15).

With respect to the method claims 73-82 and 88-89, New ('28436) discloses methods to treat a patient with a disease that comprises the administration of the above-mentioned composition, wherein the composition *enhances the absorption of the active principal across the intestinal walls* (claims 26-28). Thus, the method of using aromatic alcohols to enhance absorption was known as well.

New ('28436) differs from the instant claims by not explicitly reciting that the aromatic alcohol is selected from butylated hydroxy toluene (BHT), butylated hydroxy anisole (BHA), and propyl gallate.

New ('748) disclose that it is known in the art that compositions that buffer the pH of the digestive tract enhance the absorption of proteinaceous materials (abstract, claim 1). New ('748) disclose the presence of sodium bicarbonate in compositions alongside bile salts and proteinaceous materials, for methods to enhance permeation in the gut (claim 18).

Wacher et al. I and II (US 6,180,666 and US 5,962,522) teach the use of the aromatic alcohol to enhance absorption of molecules, including macromolecules based on the genus "cyclic peptides" (see e.g. claims 19 and 38; 11 and 18, respectively).

Chakravorty discloses that it is known in the art to formulate immunosuppressive drugs with BHT, propyl gallate or benzyl alcohol wherein such agents are antioxidants, and preservatives respectively (page 6, lines 25-30).

Ivanovic disclose that it is known in the art that preservatives and antioxidants such as BHT exhibit pKa's in the range 7.5 to 9. Further, Ivanovic disclose that the ratio of the amounts of ionized antioxidant to unionized antioxidant determines the final pH of the solution.

In view of the above teachings, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the benzyl alcohol in the formulation of New ('28436) with BHT or BHA or propyl gallate (including with the solubilization enhancers of New ('28436)), in view of the predictable result recognized in the art that aromatic alcohols enhance the adsorption of macromolecules such as cyclic peptides (New and Wacher et al. I and II) by adjusting the intestinal milieu to enhance macromolecular absorption. The addition of the enteric coating is deemed obvious in view of the teachings of New ('28436). Additionally, the range of aromatic alcohol:macromolecule (including 5:1, based on New's teaching of 75%

aromatic alcohol) is deemed a routinely optimizable parameter by the skilled artisan, *absent some evidence of unexpected result.*

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Allowable Subject Matter***

Claims 73-82 and 92-93 are allowed. The prior art of record, based on Applicant's arguments thereafter, were not found to reasonably teach or suggest a method of enhancing the absorption of an active macromolecule principle (e.g. peptide) which comprises an aromatic absorption enhancer chosen from propyl gallate, butylated hydroxyl toluene (BHT), butylated hydroxyl anisole (BHA) or analogues/derivatives thereof. The art was not found to teach or suggest such use thereof.

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Claims 73-82 and 92-83 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MA, 1/2/09

/Cecilia Tsang/  
Supervisory Patent Examiner, Art Unit 1654